No relationship between gastric pH, small bowel bacterial colonisation, and diarrhoea in HIV-1 infected patients

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Abstract

***Background/Aims*—Conclusive studies of small bowel bacterial overgrowth in patients with HIV-1 infection are limited. The relation was therefore determined between the quantity and species of bacteria in the proximal small intestine of HIV-1 infected patients and the presence of diarrhoea, gastric acidity, severity of immune deficiency, and clinical outcome.**

***Methods*—Bacteria in the duodenal fluids obtained endoscopically from 32 HIV-1 infected patients, 21 of whom had diarrhoea, and seven control subjects without HIV-1 risk factors were quantified and speciated. Gastric pH was determined at the time of endoscopy. Clinical follow up was performed to assess outcome.**

***Results*—Oropharyngeal Gram positive cocci were present in fluids from 28 patients (88%). Gram negative aerobic or facultatively anaerobic bacteria were present in fluids from 12 patients (38%), and strict anaerobes were detected in six patients (19%), but for both groups colony counts infrequently exceeded 10^4 colony forming units/ml. The number and species of bacteria did not correlate with the presence of diarrhoea, gastric pH, or CD4 lymphocyte count.**

***Conclusions*—Small bowel bacterial overgrowth is not common in HIV-1 infected patients, regardless of the presence of diarrhoea, and is not associated with hypochlorhydria.**

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Keywords: bacterial overgrowth; diarrhoea; HIV infection; AIDS

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Diarrhoea complicates HIV-1 infection in nearly two thirds of infected persons during the course of their disease.[1] Opportunistic infections of the small or large bowel are the usual cause of HIV-1 associated diarrhoea, especially in those patients with severe immune deficiency. Despite extensive diagnostic evaluation, however, the cause of diarrhoea is not identified in 15–50% of HIV-1 infected patients.[2–4] Among such patients, small intestinal bacterial overgrowth is an appropriate consideration, since hypochlorhydria is reported to be common in patients with AIDS,[5–8] and gastric and duodenal bacterial colonisation is associated with hypochlorhydria.[9–11] In addition, steatorrhoea and vitamin B-12 deficiency, both of which may result from small bowel bacterial overgrowth,[12] are well recognised in patients with AIDS.[13–15] While hypochlorhydria may be associated with gastric bacterial overgrowth in the setting of HIV-1 infection,[8] the relation between bacterial overgrowth in the small intestine and hypochlorhydria is unclear.

Studies of the prevalence of small intestinal bacterial overgrowth in HIV-1 infected patients have yielded conflicting results,[2 8 16–18] probably because of differences in the methods used to aspirate and culture the intestinal fluid and the clinical features of the study population including the degree of immunocompromise. Importantly, the clinical outcome of patients with bacterial overgrowth has not been assessed. Therefore the purpose of this study was to evaluate prospectively (*a*) the prevalence of small intestinal bacterial overgrowth in HIV-1 infected patients with and without diarrhoea and (*b*) the relation between the number and species of bacteria in the small bowel and the level of gastric acidity, the degree of immune deficiency, and clinical outcome.

Materials and methods

PATIENT POPULATION

Thirty two HIV-1 infected patients undergoing upper endoscopy at the University of Alabama at Birmingham between July 1995 and August 1997 comprised the study group. The study was approved by our institutional review board, and informed consent was obtained for all procedures. Twenty one patients had diarrhoea defined as more than three loose stools per day for at least one month. All patients had at least one set of negative stool tests, including cultures for pathogenic bacteria, stains, and culture for acid fast bacteria, examinations for ova and parasites, and assays for *Clostridium difficile* toxin. Seven adults less than 50 years of age without diarrhoea or a risk factor for HIV-1 infection undergoing upper endoscopy for unrelated reasons served as control subjects. Patients and controls were excluded if they: (*a*) had received antimicrobial therapy (other than trimethoprim-sulphamethoxazole, dapsone, or atovaquone prophylaxis for *Pneumocystis carinii* or macrolide prophylaxis for *Mycobacterium avium* complex) within one month of evaluation; (*b*) had used any anti-acid agent within the preceding month; (*c*) had pernicious anaemia, prior gastric acid reduction surgery, known hypochlorhydria, small bowel disease, or duodenal diverticula; or (*d*) did not produce duodenal fluid after five minutes of endoscopic observation and aspiration.

ENDOSCOPIC PROCEDURE

All patients and control subjects fasted for at least six hours before endoscopy. Patients with diarrhoea usually underwent upper endoscopy with a small bowel enteroscope (SF 100; Olympus Corporation, Lake Success, New York, USA) or paediatric colonoscope (PCF 100). Patients without diarrhoea underwent endoscopy with a standard diagnostic endoscope (GIF 130). Endoscopes were cleaned between each patient according to standard infection control guidelines.[19] The endoscope was passed under direct vision into the duodenum with minimal air insufflation and avoidance of suction. When endoscopic suction was necessary before entering the duodenum, the suction channel was vigorously flushed with tap water followed by air, and then suction was applied to remove any fluid remaining in the channel before entering the duodenum. When the second portion of the duodenum had been entered, a sterile container was placed on the suction port on the umbilicus of the endoscope and suction was applied in the most distal portion of the duodenum. When the small bowel enteroscope or paediatric colonoscope was used, aspiration was continued into the proximal jejunum. After the removal of at least 2 ml bile stained fluid, the fluid was transferred using sterile techniques to a Port-A-Cul vial (Becton Dickinson and Company, Cockeysville, Maryland, USA), and transported immediately to the microbiology laboratory. After aspiration of fluid and biopsy of duodenal mucosa, the endoscope was withdrawn to the stomach where 3 ml or more of fluid was aspirated from the fundic pool. Duodenal biopsy specimens were not obtained in control subjects. Biopsy specimens from patients with diarrhoea were analysed for microsporidia, mycobacteria, and cytomegalovirus using routine staining and immunohistochemical techniques. Gastric pH was measured with a pH meter (Radiometer PHM 82, Radiometer, Copenhagen, Denmark).

MICROBIOLOGICAL TECHNIQUES

On receipt of the transport vial, the specimens were placed into an anaerobe glove box incubator and opened under strict anaerobic conditions in an atmosphere of 95% nitrogen and 5% hydrogen. A slide was prepared for Gram staining and a 0.001 ml calibrated loop was inserted into the Port-A-Cul vial and used to inoculate the following agar media for isolation of anaerobic bacteria: Brucella agar with 5% sheep blood; Bacteroides bile esculin agar; kanamycin-vancomycin laked blood agar biplate; egg yolk agar (Anaerobe Systems, San Jose, California, USA); chocolate agar; cooked meat medium with glucose, haemin, and vitamin K1 (Remel Inc, Lenexa, Kansas, USA). For isolation of aerobic bacteria, trypticase soy agar with 5% sheep blood, MacConkey agar, chocolate agar, and brain-heart infusion broth were inoculated. Aerobic cultures were incubated under atmospheric conditions, except for chocolate agar plates, which were incubated under 5–10% CO_2. Anaerobic cultures were incubated in the glove box incubator. Specimens were examined daily, and aerobically cultured specimens were discarded after 72 hours if there had been no growth. Anaerobically cultured specimens were held for seven days. Colony counts were determined on agar for each individual isolate. For bacteria that grew in broth but not on agar, a subculture of the broth to agar was performed. Organisms that grew in subculture were speciated, and the colony count was considered to be $<10^3$ colony forming units (CFU)/ml, which was the lower limit of reported colony counts. All bacteria were identified by standard procedures in use in the University of Alabama Hospital Microbiology Laboratory. Bacterial overgrowth was defined according to previously proposed criteria[12 20] as $\geqslant 10^4$ of predominantly Gram negative anaerobes of colonic origin per ml of small bowel fluid.

Table 1 Clinical characteristics of 32 HIV-1 infected patients investigated for small bowel bacterial overgrowth

Clinical feature	*Diarrhoea (n=21)*	*No diarrhoea (n=11)*
Risk group		
Homosexual	19 (90)	9 (82)
Heterosexual	2 (10)	1 (9)
Intravenous drug use	0	1 (9)
Prior opportunistic infection	12 (57)	5 (45)
Antiretroviral therapy	17 (81)	7 (64)
Duration of diarrhoea (mean no of weeks)	15	NA
Number of stools/day (mean)	9	NA
Indications for endoscopy		
Diarrhoea	21 (100)	0
Oesophageal symptoms	0	7 (64)
Epigastric pain	0	2 (18)
Staging of Kaposi's sarcoma	0	2 (18)
Pneumocystis carinii prophylaxis		
Trimethoprim-sulphamethoxazole	12 (57)	9 (82)
Dapsone	6 (29)	0
Azithromycin	3 (14)	0
CD4 lymphocyte count, median (range)	20 (2–828)	50 (1–353)

Values in parentheses are percentages except where otherwise indicated.
NA, not applicable.

STATISTICAL ANALYSIS

Means with standard deviations and medians were used to characterise the populations. Categorical variables were compared using Fisher's exact test and continuous variables using *t* tests where appropriate. Non-parametric tests were used to compare groups without a normal distribution. Correlation coefficients were calculated using Pearson's correlation coefficient. A p value of less than 0.05 was considered statistically significant.

Results

PATIENTS

Table 1 summarises the clinical characteristics of the 32 HIV-1 infected study patients (mean (SD) age 36 (6) years). Of the 21 patients who underwent endoscopic evaluation for diarrhoea, a probable cause was identified in 10 (48%): cytomegalovirus colitis or enteritis in six and cryptosporidiosis, microsporidiosis and giardiasis, *C difficile* colitis, and intestinal *M avium* complex infection in one patient each. None of these 21 patients had received an empirical trial of antibiotics for diarrhoea.

BACTERIAL STUDIES

Bacteria were cultured from the small bowel fluids from all but three HIV-1 infected

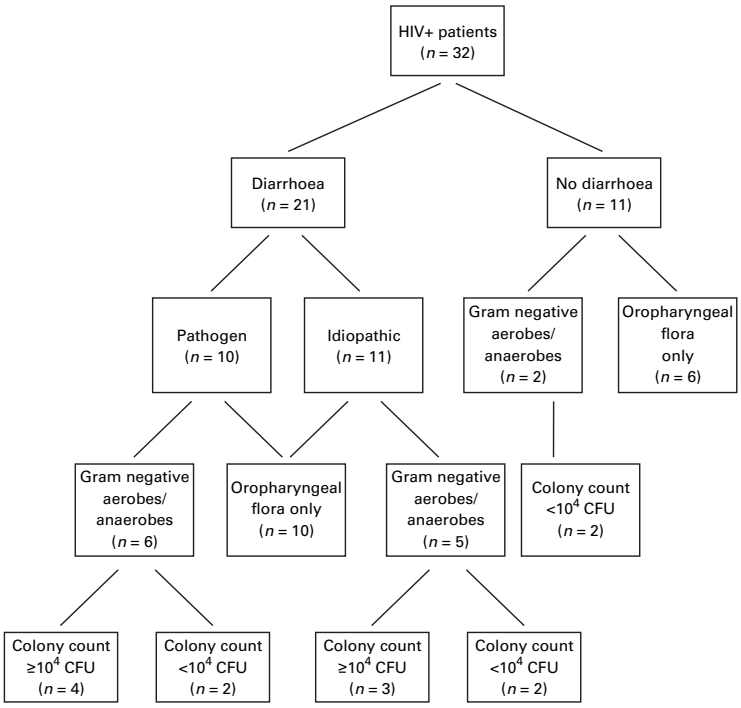

Figure 1 Schematic of the HIV-1 infected patients based on the presence of diarrhoea and type of bacterial isolate.

patients (table 2). From one of these patients only *Candida* species were cultured. The median number of different bacterial isolates was three (range zero to six), and more than one species was present in the fluids of 23 patients (72%). Eleven of 32 patients (34%) had a colony count $\geq 10^5$ CFU/ml, and 19 (59%) had colony counts $\geq 10^4$ CFU/ml. Bacteria were primarily Gram positive organisms, consistent with oropharyngeal flora.

Gram negative aerobic or facultatively anaerobic enteric bacilli were identified in the fluids from 12 patients (38%), but the colony count was $\geq 10^5$ CFU/ml in only three (fig 1). All of the six patients with colony counts $\geq 10^4$ CFU/ml had diarrhoea (cytomegalovirus enteritis or colitis in three, intestinal cryptosporidiosis in one, and idiopathic in two). Strict anaerobes were detected in six patients (19%), but only one of these was a *Bacteroides* species. Each of these six patients had diarrhoea, and in five of them a colonic biopsy yielded a potential cause: cytomegalovirus colitis in four patients and *M avium* complex in one. In all 13 patients (41%) in whom yeast (usually *Candida*) were isolated, oropharyngeal and/or oesophageal candidiasis was identified at the time of endoscopy. Colony counts for the yeast ranged from $<10^3$ to $>10^5$ CFU/ml. Prophylactic trimethoprim-sulphamethoxazole had been used by six of the 12 patients with Gram negative bacteria in the duodenal fluids, and four of the six with anaerobic bacteria. Bacteria ranging in number from $<10^3$ to 10^5 CFU/ml were isolated from all six patients receiving dapsone and were qualitatively similar to those isolated from the patients receiving trimethoprim-sulphamethoxazole.

Of the 11 patients with idiopathic diarrhoea, small bowel fluids contained Gram negative isolates in five with colony counts ranging from 1000 to 17 000 CFU/ml. An anaerobic bacterium (*Bacteroides fragilis*) was isolated from one of these 11 patients, and this was the only patient for whom both $>10^5$ CFU/ml Gram negative enteric bacteria and anaerobes were found in the duodenal fluid cultures.

Among the HIV-1 infected patients with and without Gram negative enteric bacilli in the small bowel fluids, the median absolute CD4 lymphocyte counts were similar (28/mm^3 *v* 33/mm^3; p = 0.72). Also, the number of CD4 lymphocytes did not differ significantly in patients with and without any bacterial isolate with $\geq 10^5$ CFU/ml (p = 0.64) or $\geq 10^4$ CFU/ml (p = 0.54) In addition, neither the number of bacterial isolates nor the presence of enteric bacteria appeared to have any relation to the indication for endoscopy or the presence of an infectious cause of diarrhoea (data not shown). Fourteen of 21 patients (67%) with diarrhoea underwent endoscopic examination with the enteroscope or paediatric colonoscope. Of the 11 patients with idiopathic diarrhoea, all but two underwent enteroscopy. Of these 14 patients, $>10^4$ CFU/ml bacteria were found in six and $>10^5$ CFU/ml in only two.

Table 2 lists bacteria isolated in the control subjects. In two patients fungi were identified, but in only one was the species characterised (*Candida albicans*); both patients had $<10^3$ CFU/ml. Although the bacterial species are similar to those in the HIV infected patients, colony counts tended to be lower.

Table 2 Bacterial isolates from small intestinal aspirates from 32 HIV-1 infected patients with and without diarrhoea and controls

	Patients		
Bacteria	*Diarrhoea (n=21)*	*No diarrhoea (n=11)*	*Controls (n=7)*
Gram positive cocci			
Streptococcus sp.	16 ($<10^3$–10^5)	4 ($<10^3$–4×10^3)	4 ($<10^3$–8×10^4)
Staphylococcus sp.	4 ($<10^3$–7×10^3)	2 (10^3)	2 ($<10^3$–6×10^3)
Stomatococcus sp.	—	1 (7×10^4)	—
Bacillus pumilus	1 (10^5)	—	—
Gram positive rods			
Lactobacillus sp.	6 (10^3–10^5)	4 (10^4–10^5)	1 (2×10^3)
Corynebacterium sp.	4 (10^3–4×10^4)	2 (10^3–10^4)	2 ($<10^3$–2×10^3)
Gram negative rods			
Pseudomonas aeruginosa	3 (10^3–2×10^4)	1 ($<10^3$)	1 ($>10^5$)
Escherichia coli	4 (10^3–10^5)	—	1 (2×10^3)
Klebsiella sp.	3 (10^3–10^5)	—	—
Acinetobacter sp.	1 (10^5)	—	—
Enterobacter agglomerans	1 (2×10^3)	—	—
Gram negative cocci			
Neisseria sp.	2 (2×10^3–10^4)	1 (10^3)	1 (2×10^4)
Gram negative coccobacilli			
Haemophilus parainfluenzae	—	—	1 (4×10^3)
Anaerobes			
Prevotella sp.	1 ($<10^3$)	1 (3×10^3)	—
Peptostreptococcus	1*	—	—
Veillonella sp.	1 ($<10^3$)	—	1 (10^3)
Propionibacterium acnes	1 ($<10^3$)	—	—
Bacteroides fragilis	1 (2×10^4)	—	—
Clostridia perfringes	—	—	1 ($<10^3$)

Values are expressed as number of patients and range of CFU/ml.
*Colony counts not determined.

GASTRIC PH ANALYSIS

Mean gastric pH values in HIV-1 infected patients with and without diarrhoea were not significantly different (3.0 (1.8) *v* 3.4 (2.2); p = 0.57). Mean gastric pH in the control subjects was 2.4 (range 1.8–4.1). Six (19%) HIV-1 infected patients had a fasting pH >4. One of

the patients with AIDS and hypochlorhydria (pH = 7.9) had endoscopic evidence of portal hypertensive gastropathy, which may have contributed to his hypochlorhydria.[21 22] The gastric pH was <4 in two of the three patients with pathogens identified by small bowel biopsy. Importantly, mean gastric pH did not differ among those patients with or without $\geq 10^5$ CFU/ml bacteria (4.0 (2.4) *v* 2.8 (1.7); p = 0.1) nor among those with or without Gram negative bacilli (3.3 (2) *v* 3.2 (2.1); p = 0.93). There was also no significant difference in gastric pH between patients with idiopathic diarrhoea and those in whom a cause for diarrhoea was identified (3.5 (2.3) *v* 3.3 (2.1); p = 0.81). In addition, there was no correlation between the fasting gastric pH and the CD4 lymphocyte count ($r = -0.15$; p = 0.39).

FOLLOW UP

Follow up information was available for all HIV-1 infected patients (median 8 months; range 4–33 months). No patient received antimicrobial therapy for the bacteria identified by small intestinal fluid culture. However, all patients received specific antimicrobial therapy for pathogens identified by mucosal biopsy, and in each case the diarrhoea improved or resolved. Of the five patients with idiopathic diarrhoea and Gram negative enteric bacilli identified by culture of small bowel fluid, the diarrhoea resolved in three and continued in one who had $<10^3$ CFU/ml *Pseudomonas aeruginosa*, and one who had 1.7×10^4 CFU/ml *Escherichia coli* died four weeks after endoscopy. None of the 11 HIV-1 infected patients without diarrhoea at the time of endoscopy or control subjects developed diarrhoea on follow up.

Discussion

We evaluated HIV-1 infected patients with and without diarrhoea for the presence of small bowel bacterial overgrowth and correlated these microbiological findings with gastric pH and level of immunodeficiency as assessed by CD4 lymphocyte counts. Predominantly oropharyngeal bacteria were identified in all but three of the 32 patients. Gram negative enteric bacilli were present in 12 patients (38%), 11 of whom had diarrhoea. However, five of these 11 patients had an identifiable enteric pathogen that responded to pathogen specific therapy. Although $\geq 10^5$ CFU/ml bacteria were found in 11 patients (34%), the bacteria were not aetiologically linked to the diarrhoea. Anaerobic bacteria, which play a key aetiological role in the bacterial overgrowth syndrome, were identified in 19% of the patients, but the colony counts did not achieve the level regarded as consistent with the bacterial overgrowth syndrome and only one patient had a *Bacteroide*s species.[12 21] Hypochlorhydria was present in 19% of the patients but was not related to increased numbers ($\geq 10^4$ CFU/ml) of bacteria, a specific type of bacterial isolate, severity of immune deficiency, nor the presence of a gastrointestinal pathogen.

Prior studies of small intestinal bacterial overgrowth in HIV-1 infected patients have yielded conflicting results. In these studies, culture techniques varied, methods of obtaining duodenal fluid differed, gastric pH was not consistently examined, methodology for the retrieval and culture of intestinal fluid was not always provided, and the study populations varied widely in the severity of immune deficiency and presence of diarrhoea.[2 9 17 18] When duodenal fluid was obtained in a sterile fashion, bacteria were cultured in up to 86% of patients,[8 17 18] but colony counts were usually $<10^5$ CFU/ml. Regardless of the method used to obtain duodenal fluid, when the isolated bacteria have been speciated, Gram negative bacilli or colonic-type anaerobes have not been commonly identified.

Although many of our patients were taking trimethoprim-sulphamethoxazole, this agent has no antimicrobial activity against anaerobes. Similarly, dapsone and azithromycin have no significant antimicrobial activity against anaerobes. The bacteria identified in the small bowel fluid of our patients were probably acquired from the oropharynx during intubation or through swallowing. Whether the Gram negative bacilli were similarly acquired or were restricted to the duodenum is not known, since oropharyngeal cultures were not obtained. Because there is no evidence that small bowel colonisation by Gram positive oropharyngeal flora causes duodenal disease or diarrhoea, and a polymicrobial flora composed of Gram negative bacilli and colonic-type anaerobes are critical for the development of the bacterial overgrowth syndrome,[12 21] our results suggest that the bacterial overgrowth syndrome is not common in HIV-1 infected patients.

Hypochlorhydria has been reported in HIV-1 infected patients, particularly those with more severely compromised immune function.[6] A relation between small bowel bacterial colonisation and gastric pH in HIV-1 infected patients has not been established in previous studies,[2 8 17] although Belitsos *et al*[8] detected an association between gastric pH and the presence of an intestinal parasite. In contrast, our study evaluated the relation between small bowel bacterial colonisation and gastric pH.

A strength of our study is the follow up of HIV-1 infected patients both those with diarrhoea and those without an established cause for their diarrhoea. A potential alternative cause for the diarrhoea was detected in five of the 11 patients with diarrhoea and duodenal Gram negative bacilli. Of the remaining six patients, only one had persistent diarrhoea on follow up. Similarly, of the patients with diarrhoea and anaerobic bacteria in duodenal fluids, a potential alternative pathogen was identified by biopsy in each patient. In addition, we did not identify any patient who developed diarrhoea on follow up who had Gram negative bacteria but no diarrhoea during the initial evaluation. Also, none of these patients received treatment for the bacteria identified on duodenal fluid culture.

Our study has several limitations. Firstly, we purposely studied a heterogeneous population to better define the overall prevalence of bacterial overgrowth in HIV infected patients.

Although we evaluated only 11 patients with presumed idiopathic diarrhoea, our results suggest that increasing the sample size would not have resulted in the identification of a substantial number of patients with bacterial overgrowth. Despite the severe immunodeficiency of our patients and documented presence of hypochlorhydria, we found no evidence of overgrowth even in those without diarrhoea. Secondly, since all patients did not undergo enteroscopy, we cannot exclude the possibility that bacterial overgrowth cases were missed. However, all but two patients with idiopathic diarrhoea had enteroscopy, and the bacteriological findings in these patients were similar to those in the other HIV infected patients. Similarly, it is unlikely that the use of enteroscopy in the controls would have altered the microbiological results. Thirdly, we also cannot exclude the possibility that bacterial overgrowth was present in the small bowel distal to the areas sampled. Nevertheless, if we failed to identify bacterial overgrowth for this reason, our follow up would suggest that it had no meaningful impact on outcome.

On the basis of the results of our study, routine duodenal aspiration for bacterial culture appears not to be indicated in HIV-1 infected patients with chronic unexplained diarrhoea. Likewise, an empirical trial of broad spectrum antimicrobial therapy for bacterial overgrowth in such patients is unlikely to be clinically beneficial. Hypochlorhydria may be present in about 20% of HIV-1 infected patients, but reduced gastric acidity does not appear to predispose such patients to Gram negative and anaerobic bacterial colonisation of the proximal small intestine.

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